J. Endocrinol. Invest. 22: 405-407, 1999

OPINION

The use of perchlorate for the prevention of thyrotoxicosis in patients given iodine rich contrast agents[1]

J.E. Lawrence*, S.H. Lamm**, and L.E. Braverman*

*Divisions of Genetics and Endocrinology, Brigham and Women's Hospital, Boston, MA, and
**Consultants in Epidemiology and Occupational Health, Washington, D.C., USA

The increased use of iodine rich contrast agents has led to reports of iodine-induced thyroid dysfunction (1). These compounds have large amounts of iodine. For example, diatrozoate meglumine sodium (Hypaque) has 370 mg iodine/ml (2). During coronary angiography, including angioplasty, 50 to 350 ml of contrast agent is used, which exposes the thyroid to a huge iodine load. When gastrografin is used for gastrointestinal radiographic evaluation, patients are often given 960 ml of an iodine rich solution, again resulting in a large iodine exposure. In areas of iodine sufficiency, even this large load of iodine does not usually cause thyroid dysfunction. However, in areas of relative iodine deficiency, the occurrence of thyroid autonomy is more frequent (1) and exposure to large doses of iodine in radiocontrast agents may lead to thyroid dysfunction (3). Iodine-induced hyperthyroidism, especially in the elderly, leads to increased morbidity and is more difficult to treat. Prevention of this complication would be ideal.

Potassium perchlorate is a competitive inhibitor of the sodium-iodide symporter which results in decreased entry of iodide into the thyroid (4). In view of its inhibition of the thyroid iodide trap, perchlorate was used as an antithyroid drug in the treatment of hyperthyroidism in the 1950's and 1960's with success (5). Trotter compared the toxicity of the thionamides and perchlorate and found that the total incidence of reactions to perchlorate was 2-3%. With doses greater than 1 g daily, the incidence of toxicity increased to 16-18% (6). Agranulocytosis occurred in 0.3% of the 1200 perchlorate-treated patients and in 0.94% of the 10,131 patients treated with the thionamides. Wenzel *et al.* treated patients with Graves' disease for approximately 2 years with initial doses of 900 mg daily, decreasing to 40-120 mg daily depending upon thyroid hormone levels (7). No hematologic toxicity was mentioned. However, during the mid 1960's, there were 7 cases of fatal aplastic anemia reported (8). In these 7 cases, the drug was given in relatively high doses, ranging from 600 to greater than 1000 mg daily for 3 or more months. Following these reports, the use of perchlorate essentially ceased.

A resurgence in the use of perchlorate used with PTU or methimazole has recently occurred due to its success in treating thyrotoxicosis secondary to the excess iodide in patients receiving amiodarone (9). It has also been used to demonstrate that the hypothyroidism associated with amiodarone ingestion is due to the excess iodine since hypothyroidism abates when perchlorate is given (10). Perchlorate is not recommended as therapy for iodine-induced hypothyroidism. Rather, appropriate doses of L-thyroxine should be given.

What is the frequency of thyroid dysfunction in patients receiving contrast agents? There is little data reported from the United States. In Germany, an area of mild iodine deficiency, there have been several reports. The frequency of obvious thyroid dysfunction is relatively low. In one report of 116 patients who underwent scheduled coronary angiography, 33 patients (28%) demonstrated decreased technetium uptake and increased urine iodine excretion for 3 months following angiography (11). Three patients (2.5%) developed hyperthyroidism. Interestingly, the 27 patients who were given perchlorate with methimazole (1 g sodium perchlorate and 69 mg methimazole 24 hours before and on the day of angiography) as potential drugs to prevent hyperthyroidism had normal thyroid technetium uptake and urine iodine excretion 1 and 3 months after angiography.

[1]Supported in part by Grant DK18919, NIDDK, NIH, Bethesda, MD.

Key-words: Perchlorate, iodine, thyrotoxicosis, contrast agents.

Correspondence: Dr. Lewis Braverman, Brigham and Women's Hospital, Richardson Fuller Building, Room 157, 221 Longwood Avenue, Boston, MA 02115.

Nolte *et al.* examined whether patients at high risk for iodine-induced hyperthyroidism would benefit from prophylaxis with thyrostatic drugs in a prospective-randomized study (12). Patients with thyroid autonomy were determined by a reduced TSH, blunted TSH response to thyrotropin-releasing hormone (TRH), a 10 minute 99mTc uptake more than 1.2% to exclude recent excess iodine exposure, and normal circulating free thyroid hormone levels. These 51 patients who had scheduled elective coronary angiography were randomized to receive thiamazole (20 mg/day), sodium perchlorate (900 mg/day), or no treatment. Thyrostatic therapy was started on the day before angiography and continued for 14 days. The study was performed in Northern Germany, an area of relative iodine deficiency. The results demonstrated that prophylactic thyrostatic therapy decreased the small rise in circulating thyroid hormones following coronary angiography. The incidence of mild hyperthyroidism in all 3 groups was 7.8% (4 out of 51), including one patient from each of the 2 treatment groups. Therefore, although prophylactic treatment was effective in preventing small increases in circulating thyroid hormone levels, therapy with either thiamazole or perchlorate did not completely prevent hyperthyroidism. As suggested by the authors, combination therapy might be more efficacious.

A prospective study of the effect of non-ionic contrast agents on thyroid function was carried out in two referral hospitals in Melbourne, Australia, an area of iodine sufficiency (13). Two of the 73 patients (2.7%) developed obvious clinical hyperthyroidism at 4 and 8 weeks following contrast radiography. Their serum TSH values were less than 0.01 mIU/l and their FT4 values were greater than 26.0 pmol/l (normal range: 9.0 to 26.0.) Four other patients developed evidence of biochemical hyperthyroidism, one of whom developed atrial fibrillation. This patient had a serum TSH of 0.11 mIU/l but a normal FT4 at 8 weeks. The authors found no relation between gender, volume of contrast dye, or age and changes in thyroid tests. However, the 2 patients who developed clinical hyperthyroidism were 72 and 83 years of age. This prospective study demonstrated that the occurrence of hyperthyroidism after coronary angiography in Australia is low, but that hyperthyroidism after angiography should be suspected.

In a retrospective study of 1386 patients admitted to a geriatric hospital in Melbourne, Australia, over a 20-month period, 28 patients were found to have hyperthyroidism (14). Seven patients were described who developed hyperthyroidism after administration of non-ionic contrast media. One patient may have had unsuspected hyperthyroidism prior to the study. The mean age of these patients was 80 years (range: 72 to 91) and the estimated dose of iodine was calculated to be 15 to 46 g, given in the form of iopamidol. Hyperthyroidism was recognized from 3 to 8 weeks after the radiocontrast study. Of the 7 patients with hyperthyroidism, 3 had clinically obvious goiters and another had a multinodular goiter detected by thyroid scan. Thyroid antibodies (anti-TPO) were negative in 5 of the 7 subjects who were tested. The features of hyperthyroidism were subtle, probably due to their advanced age: weight loss, psychiatric, and neuromuscular disturbances. Only 2 patients were suspected of having hyperthyroidism. Four of the 7 patients required thionamides for treatment and thyroid function resolved in 6 to 15 months. This retrospective study reemphasizes that hyperthyroidism may be missed following the administration of iodine rich contrast agents if suspicion is not maintained. In addition, it suggests that the patients who may be at risk for the development of hyperthyroidism after radiocontrast dyes likely have autonomous functioning nodules in a multinodular goiter. Such goiters are more prevalent in area of low iodine intake than in iodine replete areas and there is an increased frequency of autonomy with age (15). Since most of the patients in this study with hyperthyroidism incurred morbidity from the hyperthyroidism, resulting in readmission to the hospital and further treatment, prevention of their iodine-induced hyperthyroidism would be of value. However, since the overall frequency of hyperthyroidism is low, recognizing factors which could predict the development of hyperthyroidism, such as a nodular goiter, would be beneficial. Prophylactic treatment must be effective and without risk of serious side effects.

It seems unlikely that the aplastic anemia observed in the 1950's and 1960's would preclude the short-term use of perchlorate to prevent iodine-induced hyperthyroidism, since administration of perchlorate for a relatively short period of time has not been reported to cause significant bone marrow suppression. In addition, it is possible that the aplastic anemia occasionally seen years ago during perchlorate administration for hyperthyroidism was due to a contaminant in the inert filler of the perchlorate capsule or tablet rather than the perchlorate itself. Finally, we have recently observed that men working in a plant producing ammonium perchlorate for use as a propellant in rocket fuel are exposed chronically to up to 50 mg of perchlorate daily (determined by urine perchlorate levels) for months and years (16). No evidence of thyroid dysfunction or abnormal hematologic events were observed.

In conclusion, we believe that iodine-induced hy-

perthyroidism following the administration of radiocontrast agents in iodine sufficient areas is not common. When it does occur, it may lead to potentially serious complications. Thus far, there have been no studies which demonstrate features that can be consistently used to determine which patients will develop iodine-induced hyperthyroidism. However, elderly patients with a suppressed serum TSH or a palpable nodular goiter, especially in iodine deficient areas, seem to be at greatest risk. In addition, the older patient may be least able to tolerate the adverse hemodynamic effects of hyperthyroidism. Therefore, it might be advisable to administer the combination of perchlorate and a thionamide for a short period of time to elderly patients with a suppressed serum TSH and/or a palpable goiter.

REFERENCES

1. Fradkin J.E., Wolff J.
   Iodide-induced thyrotoxicosis.
   Medicine 1983, *62*: 1-20.
2. Roti E., Braverman L.E.
   Iodine-induced thyroid disease.
   In: Braverman L.E. (Ed.), Diseases of the thyroid.
   Humana Press Inc., Totowa, 1997, pp. 369-383.
3. Grubeck-Loebenstein B., Kronik G., Mosslacher H., Waldhausl W.
   The effect of iodine containing contrast medium on thyroid function of patients undergoing coronary angiography.
   Exp. Clin. Endocrinol. 1983, *81*: 59-64.
4. Dai G., Levy O., Carrasco N.
   Cloning and characterization of the thyroid iodide transporter.
   Nature 1996, *379*: 458-460.
5. Godley A.F., Stanbury J.B.
   Preliminary experience in the treatment of hyperthyroidism with potassium perchlorate.
   J. Clin. Endocrinol. Metab. 1954, *14*: 70-78.
6. Trotter W.R.
   The relative toxicity of antithyroid drugs.
   J. New Drugs 1962, *2*: 333-343.
7. Wenzel K.W., Lente J.R.
   Similar effects of thionamide drugs and perchlorate on thyroid-stimulating immunoglobulins in Graves' disease: evidence against immunosuppressive action of thionamide drugs.
   J. Clin. Endocrinol. Metab. 1984, *58*: 62-69.
8. Wolff J.
   Perchlorate and the thyroid gland.
   Pharmacol. Rev. 1998, *50*: 89-105.
9. Martino E., Mariotti S., Aghini-Lombardi F., Lenziardi M., Morabito S., Baschieri L., Pinchera A., Braverman L.E., Safran M.
   Short term administration of potassium perchlorate restores euthyroidism in amiodarone iodine-induced hypothyroidism.
   J. Clin. Endocrinol. Metab. 1986, *63*: 1233-1236.
10. Martino E., Aghini-Lombardi F., Mariotti S., Lenziardi M., Baschieri L., Braverman L.E., Pinchera A.
    Treatment of amiodarone associated thyrotoxicosis by simultaneous administration of potassium perchlorate and methimazole.
    J. Endocrinol. Invest. 1986, *9*: 201-207.
11. Fritzsche H., Benzer W., Furlan W., Hammerle D., Langsteger W., Weiss P.
    Prevention of iodine-induced hyperthyroidism after coronary angiography.
    Acta Med. Austriaca. 1993, *20*: 13-17.
12. Nolte W., Muller R., Siggelkow H., Emrich D., Hufner M.
    Prophylactic application of thyrostatic drugs during excessive iodine exposure in euthyroid patients with thyroid autonomy: a randomized study.
    Eur. J. Endocrinol. 1996, *134*: 337-341.
13. Conn J.J., Sebastian M.J., Deam D., Tam M., Martin F.I.
    A prospective study of the effect of nonionic contrast media on thyroid function.
    Thyroid 1996, *6*: 107-110.
14. Martin F.I., Tress B.W., Colman P.G., Deam D.R.
    Iodine-induced hyperthyroidism due to nonionic contrast radiography in the elderly.
    Am. J. Med. 1993, *95*: 78-82.
15. Berghout A., Wiersinga M., Smits N.J., Touber J.L.
    Interrelationships between age, thyroid volume, thyroid nodularity, and thyroid function in patients with sporadic nontoxic goiter.
    Am. J. Med. 1990, *893*: 602-608.
16. Lamm S.H., Braverman L.E., Li F.X., Richman K., Pino S., Howearth G.
    Thyroid health status of ammonium perchlorate worker-s: A cross-cectional occupational health study.
    J. Occup. Environ. Med. 1998, In Press.